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AN OVERVIEW ON NANOEMULSION: A NOVELDRUG DELIVERY SYSTEM

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ABSTRACT

In order to address the major issues with traditional medication administration techniques, a contemporary approach to drug administration has been created. Due to the unique characteristics of nanoscale emulsions, such as their outstanding stability, appealing look, excellent performance, and sensory benefit, interest in them has significantly increased in recent years. To improve the transport of pharmacologically active compounds, nanoemulsions are emulsions made in nanoscale diameters. Nanoemulsion typically has droplet sizes between 20 and 200 nm. The dimension and form of the particles scattered in the continuous phase is the primary distinction between an emulsion and a nanoemulsion. A full overview of a nanoemulsion system is provided by this review. These are the isotropic systems that are thermodynamically stable when two immiscible liquids are combined into one phase using an emulsifying agent like a surfactant and a co-surfactant. The focus of this paper is on presentinga broad grasp of the formulation of nanoemulsions, the preparation process, characterisation techniques, assessment criteria, and a variety of applications. Additionally, the chemical and thermodynamic durability, longevity, dispersibility, viscosity, friction, friccohesity, refractive index, % transmittance, pH, and osmolarity of nanoemulsions are examined.

KEYWORDS: Nanoemulsion, emulsion, microfluidization, High-pressure homogenization, Ultrasonication, emulsifying agent.

INTRODUCTION

Emulsions are two-phase systems in which the internal or dispersed phase of one liquid is

scattered as tiny droplets through the external or continuous phase of the other liquid.[1] They have enormous promise for the manufacturing of food, drugs, and cosmetics since they may be used to combine polar and non-polar molecules, alter the texture, flavour, and aroma of goods, and enhance the effectiveness of medical treatments.[2] Emulsions are easily changed to a variety of formulations to fulfil the specific requirements of a component or a method, which includes the dispersion of oil in water or water in oil. Emulsions offer immense promise in a variety of industries.[3] Emulsions, which are thermodynamically unstable systems, must be taken into account while working with them because, absent the addition of surface-active molecules, also known as emulsifiers, to stabilise the droplets, they will quickly separate into two discrete phases.[4]

Oil-in-water (o/w) emulsions concerning mean droplet sizes between 50 and 1000 nm are known as nanoemulsions. The words submicron emulsion (SME) and mini-emulsion are often used interchangeably because the typical droplet size is between 100 and 500 nm.[5]

Nanoemulsions are single-phase mixtures comprised of isotropic particles of two liquids that are immiscible, such as water and oil, that are held together by an intermediate coating made of the appropriate co-surfactant and surfactant. Mini-emulsions, ultrafine emulsions, and submicron emulsions are other names for them. They are thought to consist of structurally and kinetically rigid systems of submicron-sized colloidal particles.[6]

For the delivery of drugs and regulated release of physiologically relevant substances, nanoemulsions are being developed. They are potential tools for the biotechnology, drug therapy, cosmetics, and diagnostics industries.[7] Additionally, they have enormous promiseas a cutting-edge food industry delivery method for fatty acids, polyphenols, natural colors, and flavors, particularly for the production of functional foods.[8] Lipophilic active substances are poorly soluble in water, making it difficult for the food business to incorporate them into foods and beverages.[9] By employing nanoemulsions as a transportation method to alleviate the solubility problem, the bioavailability of lipophilic chemical compounds, such as vitamins and carotenoids, is also increased.[10]

About 40% of recently found drug substances are poorly water-soluble, and nano-sized carriers are recognised as effective drug delivery systems for these substances. Nanoemulsions have come to light as possible substitute drug carriers among the novel tactics.[11]

When a medication is released from a nanoemulsion, it partitions through the oil into the surfactant layer and subsequently into the watery phase. When the drug's solubilized moiety diffuses from oil and comes into touch with nearby water, nanoprecipitation occurs.[12] This significantly increases the drug's surface area, hastening the drug's dissolution in line with Noye-Whitney's equation. Thus, by gradually altering the chemical makeup of the nanoemulsion, the complexity of drug delivery at each of these steps can be influenced to construct a sustained/controlled release device.[13]

Stability and clarity are two of the fundamental properties of nanoemulsion, also known as multiphase colloidal dispersion. The oil/water interfacial tension in the dispersed phase, which typically consists of microscopic particles or droplets with a size range of 5 nm to 200 nm, is extraordinarily low.[14] Nanoemulsion can develop quickly and occasionally spontaneously, usually without the use of high energy. In addition to the surfactant, the hydrocarbon phase, and the water phase, a cosurfactant or cosolvent is frequently used.[15]

In accordance with the composition, the three most common types of nano-emulsions are likely to form:

- Oil in water
- Water in oil
- Bi-continuous[16]

The nanoemulsions' tiny droplet shape allows for constant dispersion and penetration of the active ingredients through the skin's surface.[17] Nanoemulsions have a very large surface area and a low surface tension throughout the whole emulsion system.[18,19] the components penetrate more effectively and only 3–10% of the surfactants are needed during preparation.[20]

Nanoemulsion Preparation Techniques

The best way to create nanoemulsions is with high-pressure machinery due to their very limited range of particle sizes.[21] "High-pressure homogenization" and "microfluidization," which are used in both academic and industrial contexts, are the most common methods for processing nanoemulsions.[22] Nanoemulsions can be made effectively using in-situ emulsification and ultra sonification.

High-pressure homogenization: This method creates nanoemulsions with extremely tiny particles (up to 1 nm) using a high-pressure homogenizer. The fluid is subjected to intense friction and hydraulic shear while both liquids (oily portion and aqueous portion) are mixed together and driven into an extremely small, high-pressureinput orifice (500 to 5000 psi). This results in the formation of extremely tiny emulsionparticles. A monomolecular phospholipid covering that isolates the liquid's lipophilic center from the rest of the aqueous phase may be seen on the resultant particles. The system's elevated utilisation of energy and high processing emulsion temperature is itsonly drawbacks.

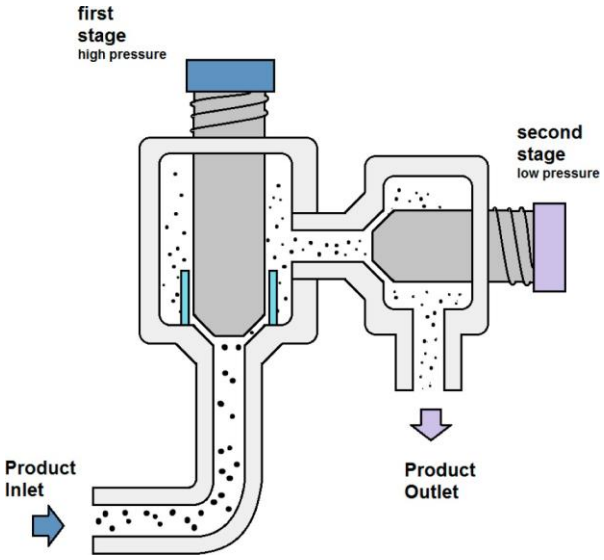

Figure High-pressure homogenizer.

Merits

- There is little batch-to-batch fluctuation during scaling up.
- Nanoparticulate for distribution of products with precision.
- The value of the item is flexible.
- Optimal utilization of thermolabile components

Micro fluidization

A microfluidizer is used during the combining process known as micro fluidization. The solution is circulated via the interaction chamber, which is composed of microscopic channels known as microchannels, using a high- pressure positive displacement pump. In the impingement region, where liquid passes through microchannels to create incredibly small submicron-scale particles. An inline homogenizer is used to blend and combine the two solutions—the aqueous phase and the oily phase—to create a coarse emulsion. The coarse

emulsion is further converted into an enduring nanoemulsion using a microfluidizer.[23]

The relationship between the chamber microfluidizer is used to repeatedly pass the coarse emulsion through until the required particle size is achieved. After that, by filtering the bulk emulsion while it is being circulated under nitrogen, the large droplets that make up a homogenous nanoemulsion are eliminated.

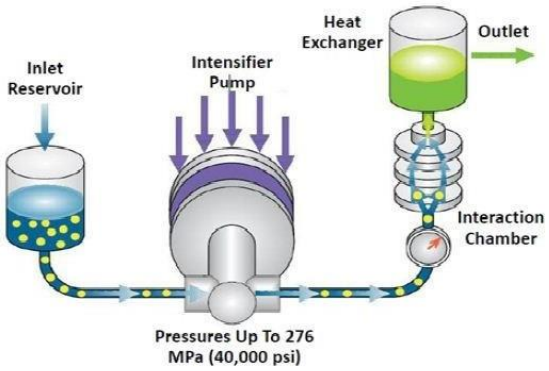

Figure: Microfluidizer.

Ultrasonication: Using ultrasonic sound frequency, nanoemulsion preparation is described in a number of research articles with the aim of reducing droplet size. Utilizing a fixed sonotrode amplitude that is greater than the ambient value at systempressures is an alternative strategy. The underlying cause of bubbles is diminished because the velocity cutoff in an ultrasonic field increases with increasing external pressure. Cavitation bubbles, however, are typically under increasing strain to break asoutside pressure increases. This implies that when cavitation takes place rather than when the pressure is in the atmosphere, the bubbles will disintegrate faster and more violently.[24]

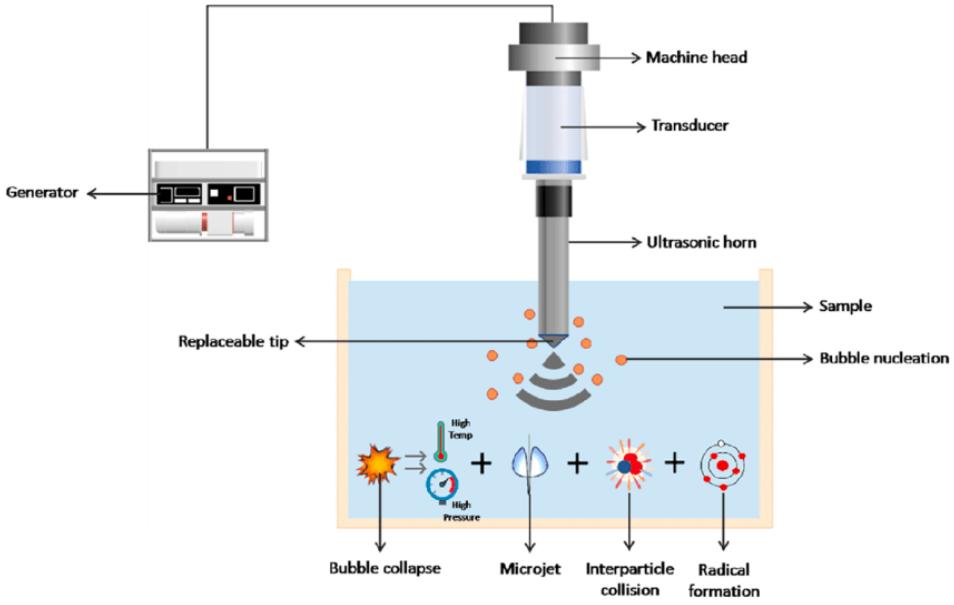

Figure: Ultrasonication

Variations in directional intensity can be automatically linked to variations in power density since cavitation is the main reason for loss of power in a low-frequency ultrasonic system. The device also uses a water jacket to maintain the right temperature.

Phase inversion method: The emulsification process, which is powered by chemical energy, caused phase transitions that led to fine dispersion. The emulsion's chemical composition can be changed while the temperature is held constant, or the opposite can occur to cause the phase transition. The conclusion was made that temperature and the breakdown of the polymer chain causes molecular changes in polyoxyethylene surfactants.[25]

Phase inversion emulsification techniques come in two different varieties: Phase inversion temperature (PIT), phase inversion composition (PIC), and catastrophic phase inversion (CPI) approaches, which include emulsion inversion point (EIP), are all components of transitional phase inversion (TPI) techniques. When parameters like temperature and composition change, it might cause changes in the binding or impulsive curvature of the surfactant, which leads to transitional phase inversion.[26,27,28] On the other hand, CPI happens when the dispersed phase is constantly injected until the dispersed phase drops combine with one another to produce two continuous/lamellar structural phases.[26] The degree of coalescence increases when the surfactant is largely in the dispersed phase, resulting in rapid phase inversion, which is required for catastrophic phase inversion to take place.[29]

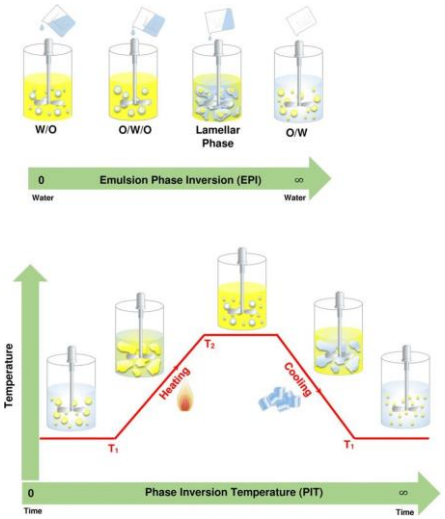

Figure: Phase inversion temperature and Emulsion inversion point.

PIT method: By altering the temperature, the surfactant's spontaneous curvature is reversed in the PIT approach. Phase inversion develops as a result, and nano emulsion is created.[30,31] Oil-in-water (O/W) emulsions are produced by mixing oil, water, and non-ionic surfactants at room temperature. Following this, when the temperature in the environment slowly rises, the surfactant's POE units start to break down, becoming increasingly lipophilic and increasing its suitability for the oily phase.[32] To alter the state of the water-in-oil (W/O) nano emulsion, the original state of the O/W emulsion goes through a phase reversal using transitional liquid crystalline or bi-continuous structures.[32] For efficient phase inversion, HLB must be rapidly cooled or heated (to create O/W or W/O emulsions, respectively).[33]

PIC method: PIC specifies that while introducing an oil-surfactant combination, one of the ingredients, such as water, must first be added to a mixture.[34] However additional nonionic surfactant types may be used, the PIC method predominantly creates nanoemulsions using nonionic surfactants of the POE type. The amount of the water portion increases and the surfactant POE chain hydrates when water begins to be added to the oil phase. This transition results in the formation of a bi-continuous or lamellar structure. The surfactant layer's frameworks, which exhibited no curvature before the addition of more water, changed to having large positive curvature after the transition composition was exceeded. Phase inversion and the formation of nanoscale droplets are the results of this curvature change. Thus, changing the system's composition causes phase inversion.[35] Other compositional elements also cause nano-size emulsion droplets by transitional phase inversion, just to how the addition of salt and pH variations do.[36,37]

EIP method: The EIP technique uses CPI procedures to achieve phase inversion.[38] Instead of the surfactant characteristics, the catastrophic phase inversion is caused by altering the fractioned quantity that makes up the dispersed phase[38] When the water phase is added to the oil-surfactant mixture, the system quickly takes on the characteristics of a W/O nano emulsion. Water droplets combine and the phase inversion point appears when more water is introduced while being continuously swirled, producing bicontinuous or lamellar structures. By dilution of excess water utilising a bi-continuous microemulsion as a bridge, a W/O system enters phase inversion to become an O/W system. Process variables, such as the rate of water addingand the rate of stirring, affect how big the resultant nano emulsion droplets are. For catastrophic phase inversion to occur, an elevated level of coalescence, and quick phase inversion to occur, the surfactant must be significantly present in the dispersed phase. In catastrophic phase inversion, surfactants consisting of tiny molecules might be utilised. These surfactants can maintain the stability of both W/O and O/W emulsions.[39,40] The surfactant behaves as an irregular (unstable) emulsion which divergesfrom Bancroft's criterion because it primarily exists in the dispersed phase at the start of a catastrophic phase inversion. According to Bancroft's recommendations, "normal emulsion" requires an emulsifier to be primarily visible during the continuous phase.[41]

Spontaneous emulsification

There are three major steps in this.

1. Producing a homogeneous organic solution by combining hydrophilic and lipophilic surfactants and dispersing them in a liquid convertible fluid.
2. The watery phase and organic phase were combined and magnetically agitated to form theo/w emulsion.
3. The water-soluble solvent was evaporated at low pressure.[42]

Technique for Solvent Evaporation

Using a separate non-solvent medicinal component, a pharmacological solution is prepared and emulsified in this method. The evaporation of the solution aids in the substance's precipitation.quantity of the buffer solution to preserve a constant size at specific periods. Using a UV spectrometer, it is possible to determine how much of the collected samples absorb.[47] One can regulate the development of crystals and the aggregation of particles by generating high shear forces with a high-speed stirrer.[43]

Nanoemulsion characteristics

- **Zeta potential:** Zeta PALS is a device that measures zeta potential. The pressure on the droplet surface is calculated using it in nanoemulsion. Emulsifiers also create surface charges, which act as a mechanical obstacle in addition to surface charges. Approaching oil droplets with zeta potential can create repelling electrostatic forces, which prevents coalescence. Zeta potential is more negatively oriented and increases with gross droplet charge and emulsion stability.
- **Polydispersity:** The ratio of the standard deviation to the mean droplet size is known as the polydispersity ratio, and it indicates how uniformly droplet size is distributed throughout the formulation. With more formulation polydispersity, droplet size consistency declines. Dynamic light scattering and polydispersity observations form the basis of the Malvern Zetasizer.[44]
- **Particle size analysis:** To evaluate particle size and scattering in nanoemulsion, the DLS method is widely utilized.[45]
- **Ratio of Drug Loading:** By combining pre-weighted nanoemulsion with the proper liquid in a 25 ml quantity, and the extract is subsequently extracted from spectrophotometric/HPLC analysis as opposed to traditional medication therapy. To identify the drug content, different columns having the right porosity are employed in the reverse phase HPLC procedure.[46]
- **TEM:** TEM can be used to examine the molecular makeup and structure of nanoemulsions.
- **Drug release in a test tube:** A dissolving device's semi-permeable membrane can be used to examine drug studies involving nanoemulsions in vitro release. The basket should be replaced with a glass cylindrical tube with a diameter and length of 2.5 cm and 6 cm, which should be tightly wrapped in the membrane that is semi-permeable. The semi-permeable membrane's surface in the cylindrical tube is coated with a drug- loaded nano emulsion. For sink conditions to be established and persistent solubilization to be preserved, the cylindrical tube must be submerged in a 100 ml solution of buffer. The research that was published can be done for a full day at 32 °C. At a 100-rpm speed, the mixing rod will spin. A one-milliliter piece of the evacuated medium is taken in, diluted, checked for quality, and then replaced with the same

Nanoemulsion applications

The majority of drug delivery methods, including topical, ophthalmic, intravenous, internasal,

and oral delivery, involve nanoemulsions. These applications make use of nanoemulsions' lyphophilic properties to dissolve medications that aren't soluble in water as well as their customizable charge and rheology to create aqueous solutions that may be administered to patients with ease.

Parenteral delivery: For intravenous administration, nano emulsion is advantageous because to the strict restrictions of this mode of administration, such as the need that a component has a size of droplet of less than 1 micrometer. Meals are just one application for parenteral nano emulsion delivery. minerals, lipids, and carbs, among other things. Parenteral nutrition using organic oils (olive, sesame, and soybean) in non-toxic PluronicF-68 nano emulsions. Research on lipid nano emulsion for parenteral drug administration is extensive. Compared to macroemulsion systems, nanoemulsion compositions have different advantages when supplied parenterally. Nanoemulsions remain in the circulatory system for a longer period than coarse particle emulsions as they are eliminated more gradually.[48]

Oral delivery: In comparison to conventional oral formulations, nano emulsion formulations for oral delivery offer a number of benefits, including greater clinical effectiveness, increased absorption, and less drug toxicity. As a result, it has been claimed that nano emulsion is the best method for delivering medications like steroids, hormones, diuretics, and antibiotics. Peptide and protein-based pharmaceuticals are extremely potent and have distinct impacts on body functions. Primaquine, when combined with an oral lipid nanoemulsion with a concentration level 25% below the standard oral dose, demonstrated strong antimalarial action in mice against *Plasmodiumbergheii* infection.[49]

Topical delivery: For a variety of reasons, topical medication delivery may be superior to other approaches. One of these is the capability to halt the medication's first-pass liver metabolism and related toxicities. Another is to administer and concentrate the medication on the affected skin or eyes. Nanoemulsion now allows for a level of topical antibacterial activity which was previously only attainable with systemic antibiotics. Medication is often used externally to treat ocular disorders that spread via the eye.[50]

Ocular delivery: The majority of drugs are given topically to treat ocular illnesses. Research on O/W nano emulsions for ocular delivery aims to eliminate poorly soluble drugs, improve absorption, and create an extended-release profile.[51]

In cosmetics: It is especially advantageous to utilise nanoemulsions with droplet diameters under 200 nm in cosmetics due to due to its large surface area permits an efficient the therapeutic ingredient's skin-contact transfer. These attractive attributes of nanoemulsions include their low viscosity and distinct visual characteristics. In the course of production, employing high-energy machinery will aid in avoiding the addition of potentially hazardous surfactants. Minimizing transepidermal water loss, improving skin safety, and increasing the penetration of active ingredients are all possible thanks to nanogel technology for creating from an oil-in-water concentration, a miniemulsion. It would be helpful for UV protection, cream moisturization, and anti-aging cosmetics.[52]

Transdermal: Transdermal indomethacin, a strong NSAID, and the anti-inflammatory benefits of a specifically formulated nano emulsion formulation were studied in rats with carrageenan-induced paw edoema. Transdermal indomethacin administration consequently demonstrated tremendous promise.[53]

In biotechnology: Only natural or aqua-organic media are used in a large number of enzymatic and biocatalytic activities. Biphasic media are also employed for these kinds of reactions. The biocatalyst is denaturized by the use of pure apolar medium. Several advantages come from using water-resistant materials.[53]

CONCLUSION

Drug delivery techniques frequently employ nanoemulsions. The formulation of nanoemulsions has many benefits, including the administration of biological, therapeutic, or diagnostic substances. The most significant use of nanoemulsion is to cover up the unpleasant flavour of greasy liquids. The concepts relating to the methods for preparing and characterizing nanoemulsions covered in this review will give the formulator a broad understanding of the methods for preparing nanoemulsions and the technologies for characterizing the prepared nanoemulsions in accordance with particular needs. In numerous fields, including those in the pharmaceutical and cosmeceutical sectors, nanoemulsions are prevalent. This is due to its adaptability as a reliable carrier system for delivering active substances to the intended delivery sites. Thus, if one wants to create a stable nano-sized emulsion, a thorough grasp of how to formulate nanoemulsions and their key characterization features is necessary. The use of nanotechnology in cosmeceutical applications is, therefore, an exciting innovation for the years to come. The research community has given it a lot of focus, which is seen in the increased number of papers in this field. By providing consumers with cutting-edge, efficient

cosmeceutical goods, this technology can help the industry stay relevant and promises sustainability in cosmetic formulations.

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